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| **ART UNIT** | **PAPER NUMBER** |
| 1642 | 11 |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trad marks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/250,056 | Marks et al |
| **Examiner** | **Group Art Unit** |
| Larry R. Helms Ph.D. | 1642 |

☒ Responsive to communication(s) filed on *20 Sep 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claim**

☒ Claim(s) *1-54* is/are pending in the applicat

Of the above, claim(s) *23-33 and 45-52* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-22, 34-44, 53, and 54* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☒ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *5, 10*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

1. The amendment to page 20, line 25 of the specification, filed 6/10/99, has not been entered because the text was not found at that position.

2. Applicant's election with traverse of Group I, claims 1-22, 34-44, and 53-54, in Paper No. 7 is acknowledged. The traversal is on the ground(s) that "a search for prior art relevant to the F5 and C1 antibodies would be expected to identify any (if such exists) relevant to the methods of use and the nucleic acids encoding the antibodies". In addition applicants argue that "a search of the prior art relevant to Groups I, II, and III entails no greater burden than a search for the art relevant to Group I alone". This is not persuasive. Applicant has provided no evidence to establish why the requirement for restriction is improper. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Further, it is doubted that applicant would readily accept the rejection of the process of the elected invention over a reference which relates only to the starting material. Clearly different searches and issues are involved in the examination of each group as set forth in paper # 4. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

3. Claims 1-54 are pending.

Claims 23-33, and 45-52 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 7.

Claims 1-22, 34-44, and 53-54 are examined on the merits.

***Oath/Declaration***

4. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

It does not state that the person making the oath or declaration has reviewed and understands the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration.

***Information Disclosure Statement***

5. The references cited in the IDS filed 9/23/99 and 7/26/99 have been considered by the examiner. It is noted that references B6, B7, B8 (9/23/99) and C40 (7/26/99) recited international search reports for PCT applications. The references cited within these search

reports are already of record and cited in the IDS and thus have been considered by the examiner. The references C40, B6, B7, and B8 have been crossed through because it is not clear that international search reports are publicly available. Accordingly, C40, B6, B7, and B8 will not appear on the face of the patent, should this application go on to issue. If applicant wishes to have the PCT applications cited in C40, B6, B7, and B8 to be considered and listed on the face of the patent, an IDS citing the PCT's under Foreign Patent Documents may be filed.

***Specification***

6. The specification is objected to because of the following reasons:

a. There are numerous spelling errors throughout the specification. For example, "-erbB2" on page 2 line 33, "10:M" on page 3 line 19, and "C-derived" on page 4 line 32.

b. The specification is objected to for it appears that either a space was inadvertently added to page 69, line 29, or some text is missing from the page.

c. The specification recites copending application USSN 08/665,202, for example, on page 31. The present status of all copending applications must be updated.

***Sequence Requirements***

7. This application contains sequence disclosures on page 40, line 22, for example, that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R.

§ 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

APPLICANT IS GIVEN THE TIME ALLOTTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response or canceling the sequences in the specification will obviate this objection.

***Claim Rejections - 35 USC § 112***

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 1-22, 34-44, and 53-54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 1-11, 14-15, 21-22, 34, and 53-54 are indefinite for reciting "F5' and "C1" because other laboratories/inventors may use the same laboratory designation to refer to different antibodies. Amendment of the claim to insert the corresponding ATCC accession number of the hybridoma which produces the antibody or to add the SEQ ID NOS of the heavy and light chain variable regions would overcome this rejection.

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b. Claim 4, 17, and 39 are indefinite for reciting "binding affinity for -erbB2 on cells of at least 10 M" or "10:M". It is not clear what affinity or units are meant. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims.

c. Claim 4 and 39 are indefinite for reciting "-erbB2" for it appears that this is a typographical error and "c-erbB2" was meant.

d. Claims 16-20, 34-44, and 53-54 are indefinite for reciting "said antibody" in claim 16, line 7. It is not clear if "said antidoby" is referring to the anti-idiotypic antibody or the antibody in line 1. In addition, it is not clear if the term "that" in claim 16, line 8 is referring to "said antibody" in line 7 or anti-idiotypic antibody in line 5 or the antibody in line 1. These terms are indefinite because proper antecedent basis is lacking in the claims. See 37 CFR 1.75(d)(1) and

MPEP § 608.01(o). Due to this confusion it is not clear what limitations are suggested in claim 16 and therefore the limitations suggested in lines 7-9 of claim 16 are unsearchable.

e. Claim 16 is indefinite for reciting "least" in line 2. It is not clear if "least" or "at least" was intended.

f. Claim 16 is indefinite for reciting "polypeptide sequence" for it is not known what is meant by the phrase. The term "sequence" refers to information describing a nucleic acid or amino acid sequence. Information is not a chemical structure, therefore, it is not clear how "sequences" can be linked to polypeptide molecules. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claim. Replacing the term "sequence" with molecule would obviate this rejection.

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g. Claims 53 and 54 are indefinite for reciting "pharmaceutical composition" because the exact meaning of the phrase is not known. It is not clear whether the term "pharmaceutical" is an intended use of the composition or whether it describes structural or functional properties of the composition. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claims. Removal of the term "pharmaceutical" before composition would obviate this rejection.

h. Claims 21 and 22 are indefinite for it is not clear if these claims are an apparent duplication of claims 14 and 15 or claims 21 and 22 are dependent on claim 16. As written, it is impossible for one skilled in the art to determine the metes and bounds of the claim.

I. Claims 12-15, 21, 22, 43, and 44 are indefinite for reciting "has" for it is not clear what is meant by the word. Does this mean having a portion, having the exact sequence (consisting of), or having the exact sequence and extra sequences (comprising). As written, it is impossible for one skilled in the art to determine the metes and bounds of the claim. Amending the claims to recite "consisting of" or "comprising" would obviate this rejection.

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claim 1-13, 16-20, 34-42, 53-54 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an internalizing antibody that specifically binds to a c-erbB2 receptor epitope where the antibody consists of or comprises an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2 and chimeric molecules comprising an effector molecule attached to the antibodies consisting of or comprising SEQ ID NO:1 or SEQ ID NO:2, and compositions comprising a pharmacological excipient and the said antibodies, wherein said antibodies contain all six CDRs from SEQ ID NO:1 or SEQ ID NO:2 appropriately spaced between framework regions, does not reasonably provide enablement for all antibodies that specifically bind to a c-erbB2 receptor epitope wherein said antibodies have conservative substitutions, share at least 70% sequence identity to SEQ ID NO:1 or SEQ ID NO:2, or the antibodies differ from the amino acid sequence of SEQ ID NO:1 or SEQ ID N O:2 by no more

than 30 residues, or the antibody comprises at least 10 contiguous amino acids from SEQ ID NO:1 or SEQ ID NO:2 that specifically binds a c-erbB2 receptor, or antibodies which do not contain six CDRs and bind antigen, or pharmaceutical compositions comprising the antibodies. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Claims 14, 15, 21, 22, 43, and 44 are enabled for antibodies which have amino acids of SEQ ID NO:1, for example in claim 14, because the term "has" is being interpreted as having all of the sequence (consisting of) or having all of the sequence plus additional sequences (comprising) (see 112 2nd paragraph rejection).

a. Factors to be considered in determining whether undue experimentation is required, are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

b. The claims broadly encompass internalizing antibodies that specifically binds to a c-erbB2 receptor wherein said antibodies are selected from antibodies having an unspecified amount of conservative substitutions or share 70% sequence identity with the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2 and have a binding affinity for the c-erbB2 on cells

of at least 10 M. Claim 5 broadly encompasses changes in the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2 by no more than 30 amino acid residues, but does not stipulate where these changes are allowed in the protein. Claim 16 broadly encompasses production of an anti-idiotypic antibody produced by presenting an antigen of an antibody that specifically binds c-erbB2 receptor comprising at least 10 contiguous amino acids in SEQ ID NO:1 or SEQ ID NO:2. The claims broadly recite the antibodies that specifically bind to the c-erbB2 receptor comprises one or two or three CDRs (claims 6-13, 19-20, and 41-42).

c. The specification teaches the production of single chain antibodies (F5 and C1) to the c-erbB2 receptor that are internalizing containing the amino acid sequence of SEQ ID NO:1 or SEQ ID NO:2. The specification contemplates the F5 and C1 antibodies bind to the same epitope (page 69, line 26), however, the specification lacks the disclosure of the epitope to which the antibodies F5 and C1 bind. The specification also teaches using a composition assay to confirm that the F5 and C1 antibodies recognize the same epitope. The specification recites "conservative substitutions" (pages 8-9, bridging paragraph) but apparently lacks any definition of the number of conservative substitutions that can be allowed in the amino acid sequence and still retain antigen binding. The specification defines "identity" of the amino acid sequence as 'two or more sequences or subsequences that are the same or have a specified percentage of the amino acid residues or nucleotides that are the same, when compared and aligned for maximum correspondence, as measured using one of the following sequence comparison algorithms or by visual inspection" (page 9, last paragraph). The specification then teaches numerous algorithms

for calculating 'identity' (pages 10-12). It is not clear which algorithm was used to calculate "70% sequence identity". The specification teaches the CDR randomization of antibody where partial or entire CDRs are randomized, for example the CDR 1 and 2 of VL and CDRs 1, 2, and 3 of VH (page 29, lines 15-16). The specification apparently lacks a description of antibodies that contain only one, two, or three CDRs and bind antigen.

d. It is well established in the art that the c-erbB-2 receptor is a cell surface glycoprotein (page 172, first full paragraph) (Ishida et al., Jpn. J. Cancer Res., 85:172-178 (1994)). The claimed antibodies are known to bind to an epitope on the c-erbB2 receptor, however, the epitope structure was not disclosed in the specification. It was not disclosed if the epitope is a continuous linear epitope of amino acids or a discontinuous conformational epitope of amino acids or if the epitope contains carbohydrate moieties.

e. As taught in Greenspan et al (Nature Biotechnology 7:936-937 (1999)) defining epitopes is not as easy as it seems (page 937). Epitopes have been defined in terms of the spacial organization of residues that make contact with a ligand and the structural characterization of the molecular interface for the binding of the molecules to define the epitope boundaries (page 937 middle of page). The epitope defined in this manner will likely include residues that contact the ligand but are energetically neutral or even destabilizing to binding. "In addition, a priori it will not include any residue that makes no contact with a ligand but whose substitution may profoundly effect ligand recognition through influence on the stability of the free form of the macromolecule, or participation in long-range allosteric effects". "Even when the residues

making contacts with ligands are known with certainty, say from the crystal structure of the complex, the question remains with regard to the energetic involvement of each residue (page 936 right column, first paragraph). Therefore, "amino acids should be recognized to have multiple ways of contributing to a noncovalent interaction" (page 937, middle of page). The specification teaches epitope mapping of the F5 and C1 using competition assay (page 69, lines 25-26 and figure 2), however, the results are not clear that the antibodies do in fact bind the same epitope. As evidenced by Greenspan et al a number of factors not primarily related to the contours of the contacts of the molecules contribute to the free energy change, sometimes profoundly.

f. Recognition of carbohydrate moieties bound by antibodies is a complex and unpredictable task. Unlike linear amino acid epitopes, which can be readily synthesized in vitro and against which other antibodies can be readily made, carbohydrate epitopes are more complex and difficult to synthesize. Knight (BioTechnology Vol 7 No 1, Jan 1989) likens this task to "wrestling with a cloud". She states that "prediction and control of the expression of oligosaccharide remains elusive and threatens to remain so from some time" and the challenge is "a daunting one". Knight goes one to explain that "the structure of carbohydrates is much more complex than that of proteins. Dwek likens the task of sequencing a carbohydrate to "simultaneously sequencing 40 or 50 proteins". Because carbohydrate structures are a branching series of linked rings, they can combine in many more ways that can linear peptide chains. For comparison, consider that while three amino acids can combine in only six ways, three

carbohydrate monomers can form over 1,000 different trisaccharide structures" (see page 39, first column, third and fourth full paragraphs). One skilled in the art would reasonably conclude that, even if one had known that the F5 or C1 epitope comprised carbohydrate moieties, the synthesis of potential carbohydrate moieties would require undue experimentation.

g. Even if one skilled in the art were able to identify a region of a glycosylated protein that bound a particular antibody, Knight teaches the unpredictability of knowing the exact structure found in that glycoprotein. Knight states that "on top of this amazing diversity, nature adds what glycobiologists call "micro heterogeneity" in the form of discrete subsets -glycoforms- of a glycoprotein. These may have difference physical and biochemical properties." One skilled in the art would reasonably conclude that these different physical and biochemical properties encompass expression of different epitopes. Knight summarize that "the "demographics" of its glycoform population determine the composite activity of a glycosylated compound. According to Rademacher, Parekh and Dwek, "Any given glycoprotein that consists of different glycoforms will... have a composite activity, reflecting a weighted average of the activity and incidence of each glycoform" (page 39, third column, second full paragraph).

h. Moreover, it is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in

maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

I. Further, as evidenced by Adair et al. (PCT GB90/02017) transfer of CDR regions alone are often not sufficient to provide satisfactory binding activity in the CDR-grafted product (p. 4). Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substitution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986). It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions have the required binding function. In addition it is not clear if an antibody that comprises least 10 contiguous amino acids from the polypeptide as set forth in SEQ ID NO:1 or SEQ ID NO:2 would bind specifically to the c-erbB2 receptor as recited in claim 16.

j. Claims 4, 17, and 39 recite 70% sequence identity, however, sequence alignment between two sequences has no common meaning in the art. See George et al; "Current Methods in Sequence Comparison and Analysis", in Macromolecular Sequencing and Synthesis, Selected Methods and Applications, pages 127-149 1988, Alan R. Liss, Inc and Barton et al "Protein Sequence Alignment and Database Scanning" in Protein Structure Prediction, A Practical Approach, 1996 IRL Press at Oxford University Press, Oxford, UK, pages 31-63). Barton et al teach that the "results of the analysis are entirely dependent on the choice of scoring results" (page 130, col 1-2, bridging paragraph). George et al teach that percent sequence identity is not an objective property of molecules but is a value arrived at by using algorithms (page 130, columns 1-2, bridging paragraph). One skilled in the art would reasonably conclude that methods of aligning amino acid sequences also depends on the choice of scoring results and the use of algorithms. The scoring of gaps when comparing one amino acid sequence to another introduces uncertainty as to the percent of similarity and the manner of alignment between two sequences.

k. The specification teaches a variety of algorithms for sequence (see pages 9-12) however the specification apparently lacks any particular guidance or specific method for determining 70% sequence identity. Therefore, it remains unclear what sort of alignment is allowed (i.e., gaps, mismatches) and which amino acid residues are considered to be similar. . Thus, one cannot therefore determine how to make and use molecules which have "70% sequence identity".

l. Claims 53 and 54 are drawn to a pharmaceutical composition comprising a pharmaceutical excipient and a chimeric molecule. Enablement of a "pharmaceutical composition" is considered to rest on a teaching of in vivo administration for purposes consistent with the intended use disclosed in the specification. The disclosed intended use for the claimed pharmaceutical compositions/vaccine is for the treatment of c-erbB2 bearing cancer cells. Thus, the nature of the invention is an immunogenic/therapeutic composition used in the treatment of c-erbB2 positive carcinoma.

m. Although the specification discloses the claimed composition, and general methods for formulating compositions in pharmaceutically acceptable carriers, there is insufficient guidance which would enable one skilled in the art to use the claimed compositions for their intended purpose, viz., for the treatment of c-erbB2 positive carcinoma. .

n. At the time the invention was made, pharmaceutical compositions/vaccines comprising the claimed antibodies were not routinely used for the treatment of c-erbB2 positive carcinoma. The specification lacks guidance by way of general methods or working examples which teach an amount of the antibodies which would be used for this purpose. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art, such as immunotherapy of the treatment of c-erbB2 positive carcinoma. Further, it is not routine in the art of treatment of c-erbB2 positive carcinoma therapy to use compositions analogous to the claimed compositions for this purpose. Accordingly, there is no objective basis upon which the skilled artisan would reasonably be able to determine or predict an amount of the claimed

composition/vaccine effective for its intended use. Therefore, undue experimentation would be required to make and use the invention. Removing "pharmaceutical" before composition would obviate this portion of the rejection.

o. In summary, the specification provides inadequate direction or guidance regarding how to produce the antibodies as broadly defined by the claims as well as the epitope the antibodies bind to in order to produce the claimed antibodies. Taken in view of the references cited above in support of the unpredictability of the art and the inadequate guidance of the specification, undue experimentation would be required to make and use the invention commensurate with the scope of the broadly written claims. Therefore, in weighing the factors to be considered in determining whether or not the practice of a claimed invention would require "undue" experimentation, as set forth in In re Wands (8 USPQ 2d at 1404), the weight of the analysis clearly favors a finding of "undue" experimentation.

p. Amending the claims to an internalizing antibody that specifically binds to a c-erbB2 receptor epitope where the antibody consists of or comprises an amino acid sequence selected from SEQ ID NO:1 or SEQ ID NO:2 and chimeric molecules comprising an effector molecule attached to the antibodies consisting of or comprising SEQ ID NO:1 or SEQ ID NO:2, and compositions comprising a pharmacological excipient and the said antibodies, wherein said antibodies contain all six CDRs from SEQ ID NO:1 or SEQ ID NO:2 appropriately spaced between framework regions may be sufficient to obviate the rejection.

***Biological Deposit***

12. Claims 1-13, 16-20, 34-42, and 53-54 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

a. It is unclear if a cell line which produces antibodies having the exact chemical identity of F5 and C1 are known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell lines, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell lines; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

b. For example, very different $V_H$ chains (about 50% homologous) can combine with the same $V_K$ chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different $V_H$ sequences combine with different $V_K$ sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar

immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species F5 and C1. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

c. The specification is lacking the date of deposit, ATCC#, and the address of the ATCC as well as assurances that the hybridomas producing the antibodies will become publicly available upon issue of the patent. See 37 CFR 1.801-1.809.

***Claim Rejections - 35 USC § 102***

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

14. Claims 1-22, 34-44, and 53-54 are rejected under 35 U.S.C. 102(b) as being anticipated by Maier et al (Cancer Research, 51:5361-5369, 1991).

a. The claims recite an internalizing antibody that specifically binds to a c-erbB2 receptor epitope bound by F5 or C1. Further embodiments are a chimeric molecule that binds to a cell bearing a c-erbB2, such that the chimeric molecule comprises an effector molecule attached to

the antibody of claim 1 or 16, further the effector is selected from the group consisting of a cytotoxin, a label, a radionuclide, a drug, a liposome, a ligand, and an antibody, further the cell is a breast cancer cell, and compositions comprising a pharmaceutical excipient and the chimeric molecule or antibody. Due to the indefinite nature of claim 16 (see 112 2nd above) the limitations encompassed by the claim and claims which depend on it were not searchable.

b. Maier et al teach the monoclonal antibody, TA1, which is an internalizing antibody which specifically binds to the c-erbB2 receptor (see abstract). Maier et al also teach the radiolabelling of the TA1 antibody (see p 5362, radiolabelling of antibodies) as well as immunotoxins (page 5362, Antibodies and Immunotoxins), and gold sols (see page 5362) and the specific binding of the gold sol labeled TA1 to SKBr3 breast cancer cells (see p 5363, 1st paragraph). Maier et al also teach the TA1 antibody in PBS (page 5362, Flow Cytometry). Maier et al is silent concerning the amino acid sequence and the particular epitope bound by the TA1 antibody.

c. No added weight is given to the intended use phrase "pharmaceutical composition" in the claims (see 112 2nd rejection above). Therefore Maier et al's composition of the TA1 antibody in PBS meets the limitations of claims 53 and 54.

d. Because the claims recite an antibody by laboratory designation, SEQ ID NO:1 or 2, that is internalizing, binds to a c-erbB2 receptor epitope that is not disclosed and Maier et al is silent as to the sequence of the TA1 antibody and its c-erbB2 receptor epitope, it is the Examiner's position that Maier et al have produced an antibody that is directed to the same

antigen c-erbB2 as recited in the claims, that is internalizing and that this antibody has the same properties as that claimed in that it can be used to detect the presence of the same c-erbB2 receptor antigen. One of ordinary skill in the art would reasonably conclude that Maier et al's antibody also possesses the same binding to the c-erbB2 receptor epitope, therefore, it appears that Maier et al have produced an antibody that is identical to the claimed antibody F5 or C1 which can be used to assay the same c-erbB2 receptor epitope. In regards to claims reciting a particular sequence, Maier et al is silent about the TA1 sequence. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibody F5 or C1 or the particular epitope of c-erbB2 receptor or sequence of the antibodies with the antibody and the c-erbB2 receptor epitope of Maier et al, the burden of proof is upon the Applicants to show a distinction between the structural and functional characteristics of the claimed F5 or C1 antibody and the c-erbB2 receptor epitope and the antibody and the epitope of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

***Summary***

15. No Claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The

examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

Respectfully,

Larry R. Helms Ph.D.

JBurke

JULIE BURKE
PRIMARY EXAMINER

Application No.: 09/250056

# NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).

☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).

☐ 7. Other: _____

## Applicant Must Provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.

☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216
For CRF Submission Help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

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